

Remarks

Claims 70-79, 81 and 83-91 are pending in the subject application. Applicants gratefully acknowledge that prosecution has been reopened and that the after-final Amendment filed December 2, 2010 has been considered and entered into the record. Although not indicated on the Office Action Summary page, Applicants note that claim 78 is withdrawn from consideration. Accordingly, claims 70-77, 79, 81 and 83-91 are pending and are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejections under 35 U.S.C. § 103 (a) (over Velardi *et al.* and Eisenthal *et al.*) and 35 U.S.C. § 102(b) (over Shin *et al.*). Applicants also gratefully acknowledge the Examiner's indication that claims 70-79, 81 and 83-87 are allowed.

At the time this response is considered, Applicants respectfully request the courtesy of an interview in order to address any issues that may remain in this application.

Claims 88 and 90-91 are rejected under 35 U.S.C. § 102(b) as anticipated by Kim *et al.* (1997) as evidenced by Shin *et al.* (1999) and by alleged admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26. The Office Action claims that Kim *et al.* teach anti-p58 KIR monoclonal antibodies (mAbs) that interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58. Applicants respectfully assert that the cited references do not anticipate the claimed invention.

At the outset, Applicants respectfully request that the next Office Action clarify what it considers to be "admissions" within the as-filed specification. The sections discussed in the Office Action provide definitions as to the meaning of "neutralize KIR mediated inhibition" and "neutralize KIR-mediated inhibition of NK cell cytotoxicity". Applicants note that the quoted sections of the specification are drawn from the "Detailed Description of the Invention" and are contained in the section directed to a discussion of novel antibodies and fragments or derivatives thereof that bind common determinants of human inhibitory KIR receptors, preferably a determinant present on at least two different KIR2DL gene products, and cause potentiation of NK cells expressing at least one of those KIR receptors.

Turning to the rejection of record, the Office Action asserts that Kim *et al.* teach anti-p58 KIR mAbs that interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876). The Office Action further argues that although the reference does not explicitly teach that the neutralizing anti-p58 mAbs bind to KIR2DL1 and KIR2DL2/3, the evidentiary reference Shin *et al.* teach that an mAb that has its epitope in the HLA-binding region in p58 KIR may be the most effective mAb for blocking the interaction between p59 KIR and HLA-C, and that HLA-C recognizing receptor that is inhibitory is the p58 KIR belonging to KIR2DL group comprised of KIR2DL1 and KIR2DL2/3. Therefore, the Office Action argues, the claimed antibody appears to be the same or similar to the antibody of the prior art absent a showing of differences. Applicants respectfully disagree.

First, Kim *et al.* themselves do not teach, report or use any antibodies (Kim *et al.* use only recombinant KIR and HLA-C proteins). Rather, Kim *et al.* make reference to previous studies that literature that use antibodies that bind to KIR (see, for example, the passage at page 3876 emphasized in the Office Action). The passage at page 3876 of Kim *et al.*, to which the Office Action appears to refer, cites references numbered 22, 23 and 36, which respectively correspond to Moretta *et al.* (1993) J. Exp. Med. 178: 597, Vitale *et al.* (1995) P.N.A.S. USA 92:3536 and Ciccone *et al.* (1994) Eur. J. Immunol. 24:1003. This passage refers solely to two antibodies, EB6 and GL183, which do *not* bind *both* KIR2DL1 and KIR2DL2/3 and is reproduced below (emphasis added).

Human NK clones can be grouped according to their HLA-C recognition and Ab-binding properties (22). A group of NK clones that is reactive with **mAb EB6** recognizes HLA-Cw4 and related alleles, including HLA-Cw2, -Cw5, and -Cw6. A second group of NK clones reactive with **mAb GL183** recognizes HLA-Cw3 and related alleles, including HLA-Cw1, -Cw7, and -Cw8 (22, 23, 33, 34). NK clones negative for p58 KIRs were also found to be specific for different alleles of class I MHC molecules (35). **Specific interaction between HLA-C and p58 KIRs was suggested by Ab blocking experiments (22, 23, 36).** Either anti-class I MHC or anti-p58 KIR mAbs were found to interfere with class I MHC-mediated protection of target cells. Direct evidence for specific recognition of target cells by NK receptors was provided by the binding of a soluble form of p.58 KIRs to cells transfected with the cognate HLA-C subtype (26) and by direct binding between a recombinant

soluble p58 KIR and recombinant soluble HLA-Cw4 (37). The soluble KIR forms a 1:1 complex with the HLA-Cw4 molecule.

With regard to cited references 22, 23 and 36, Moretta *et al.* (1993), submitted in an Information Disclosure Statement (IDS) dated September 21, 2006, makes use of EB6 and GL183 (and XA141, an IgM specific for the EB6 molecules, see abstract). Vitale *et al.* (1995), provided with the accompanying IDS, uses the same EB6, GL183 (and XA-141) antibodies as Moretta (1993). Finally, Ciccone *et al.* (1994), also provided with the accompanying IDS, did not use anti-KIR antibodies but rather anti-HLA-C antibodies 6A4 and A6-136 mAb, which respectively bind HLA-cw4 or HLA-cw3. Consequently, Kim *et al.* refer to antibodies EB6 and/or GL183, both of which have been previously discussed in Applicants' responses dated December 2, 2010 and October 28, 2010. EB6 binds KIR2DL1 but *not* KIR2DL2/3. GL183 in turn binds KIR2DL2/3 but *not* KIR2DL1 (see paragraph bridging pages 524-525 of Shin *et al.*). Kim *et al.* therefore do not anticipate the present claims which require binding to both KIR2DL1 and KIR2DL2/3.

Indeed, the "evidentiary reference" cited in the Office Action clearly indicates that this is the case. Shin *et al.* report a number of antibodies that **are not cross-reactive with both KIR2DL1 and KIR2DL2/3** (see, *e.g.*, Table 1 and page 524 of Shin *et al.*) and Shin *et al.* clearly teach that GL183 and EB6 do not bind to both KIR2DL1 and KIR2DL2/3. Shin *et al.* report two antibodies, A210 and A803g, that *do* bind both KIR2DL1 and KIR2DL3, but *neither of them inhibited a KIR2DL*, as summarized by the following passages:

Previously, we obtained three recombinant P58 KIR or p50 KAR proteins, KAR-K1 (KIR2DS4), KIR-K6 (KIR2DL1), and KIR-K7 (KIR2DL3)....while A210 and A803g bound to all three recombinant proteins. (see Shin *et al.*, Abstract, lines 3-8)

Among the existing MAbs, EB6 and GL183 are able to interfere with the binding between p58 KIR and HLA-C and to block the inhibitory signal transmitted through p58 KIR (6-8). So NK cytotoxicity is increased when EB6 or GL183 is added to a co-culture system of NK cells and HLA-C expressed target cells (6-8). With the MAbs produced in this study, it was examined whether MAbs could interfere with the binding between p58 KIR and HLA-C. **However, no MAbs interfered with the binding or blocked the inhibitory signal transmitted through p58 KIR (data not shown)**...Moreover, **broad reactivity in our MAbs implied that their epitopes did not exist on the HLA-binding region in p58 KIR.** (emphasis added; see Shin *et al.*, page 526, first full paragraph).

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Kim *et al.* (1997) as evidenced by Shin *et al.* (1999) is respectfully requested.

Claims 88 and 89 are rejected under 35 U.S.C. § 103(a) as obvious over Kim *et al.* (1997) in view of Harlow and Lane (1988). The Office Action states that Kim *et al.* teach anti-p58 KIR mAbs that were found to interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58. The Office Action asserts that Harlow and Lane teach that PBS or similar isotonic solutions are commonly used buffers for storing purified antibodies.

The Office Action asserts that Kim *et al.* teach anti-p58 KIR mAbs that interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876). The Office Action further argues that Harlow and Lane teach that PBS or similar isotonic solutions are commonly used buffers for storing purified antibodies, and that consequently it would have been obvious to place the antibodies of Kim *et al.* in PBS. Applicants respectfully assert that the claimed invention is not obvious over the cited references.

Obviousness requires a teaching or suggestion of all limitations in a claim. *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). As discussed above with respect to the rejection under 35 U.S.C. § 102(b), Kim *et al.* themselves do not report or use any antibodies (using only recombinant KIR and HLA-C proteins). Rather, Kim *et al.* make reference to previous studies that literature that use antibodies that bind to KIR (see, for example, the passage at page 3876 emphasized in the Office Action) and this passage, in turn, refers solely to two antibodies, EB6 and GL183. As discussed above, these antibodies do *not* bind *both* KIR2DL1 and KIR2DL2/3. Consequently, Kim *et al.* do not disclose antibodies that meet the limitations of the present claims which require binding to both KIR2DL1 and KIR2DL2/3 and the teachings of Harlow and Lane do not remedy this defect in the teachings of Kim *et al.* Accordingly, it is respectfully submitted that a *prima facie* case of obviousness has not been established and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 88, 90 and 91 are rejected under 35 U.S.C. § 103(a) as obvious over Shin *et al.* (1999) in view of Kim *et al.* (1997) and by admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26. The Office Action indicates that Shin *et al.* teach that HLA-C-recognizing receptor that is inhibitory is the p58 belonging to KIR2DL group comprised of KIR2DL1 and KIR2DL2/3. Shin *et al.* is also cited as teaching that the “mAb that has its epitope in the HLA-binding region in p58 KIR may be the most effective mAb for blocking the interaction between p58 KIR and HLA-C that it is known that both the  $\gamma$ 2 and  $\gamma$ 3 domains are involved in the interaction between p58 KIR and its ligand, HLA-C.” Shin *et al.* is also cited as teaching the method of mAb production via conventional hybridoma technology of Kohler and Milstein as well as methods for assessing the ability of the mAb to inhibit p58-mediated inhibition of NK cell cytotoxicity. The Office Action claims that Kim *et al.* teach that a polypeptide consisting of the  $\gamma$ 2 and  $\gamma$ 3 domains can be recombinantly produced, as it folds properly. The Office Action also states that Kim *et al.* teach that their experiments suggest that both Ig domains of p58 are necessary for HLA-C binding and that the binding site on KIR might be the exposed region at the interface between the N- and C-terminal  $\gamma$  domains. The Office Action concludes that Kim *et al.* teach anti-p58 KIR mAbs that were found to interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58. Applicants respectfully assert that the claimed invention is not obvious over the cited references.

The Office Action argues that Shin *et al.* teach that HLA-C recognizing receptor that is inhibitory is the p58 belonging to KIR2DL group comprised of KIR2DL1 and KIR2DL2/3, that a mAb that has its epitope in the HLA- binding region in p58 KIR may be the most effective mAb for blocking the interaction between p58 KIR and HLA-C, and that it is known that both the  $\gamma$ 2 and  $\gamma$ 3 domains are involved in the interaction between p58 KIR and its ligand HLA-C. The Office Action further argues that Kim *et al.* teach anti-p58 mAbs that were found to interfere with class I-mediated protection of target cells, *i.e.*, they are capable of neutralizing KIR-mediated inhibition of NK cell cytotoxicity in NK cells expressing p58 (especially page 3876). The Office Action then concludes that it would have been *prima facie* obvious to have made more mAbs by the conventional hybridoma monoclonal antibody methodology taught by Shin *et al.* and to have tested for antibodies

that bind to both KIR2DL1 and to KIR2DL2/3 and to have further tested these antibodies for the ability to neutralize KIR-mediated inhibition of NK cell cytotoxicity.

First, neither Shin *et al.* nor Kim *et al.* provide any motivation for seeking an antibody that binds to both KIR2DL1 and to KIR2DL2/3 and neutralizes KIR-mediated inhibition of NK cell cytotoxicity. While Shin *et al.* may have tested different antibodies for binding to various KIR molecules once those antibodies were produced, Shin *et al.* provide no suggestion that one should select for antibodies that bind to KIR2DL1 and KIR2DL2/3 and neutralize KIR-mediated inhibition of NK cell cytotoxicity. Indeed, Shin *et al.* teach that they were unable to identify mAbs interfered with the binding or blocked the inhibitory signal transmitted through p58 KIR (see page 526, first full paragraph). Thus, it is also respectfully submitted that one of ordinary skill in the art would not have had a reasonable expectation of success in making antibodies that bound to both KIR2DL1 and to KIR2DL2/3 and neutralized KIR-mediated inhibition of NK cell cytotoxicity.

Furthermore, the Office Action states that Shin *et al.* teach that an mAb that has its epitope in the HLA-binding region in p58 KIR may be the most effective mAb for blocking the interaction between p58 KIR. However, there is no indication that Shin *et al.* do anything other than simply consider KIR2DL1 and KIR2DL2/3 separately, which is not surprising given that these receptors bind to different ligands (HLA-cw4 and HLA-cw3, respectively) in a mutually exclusive fashion. While KIR2DL1 and KIR2DL2/3 share high homology, the homology is lower in the HLA binding regions, and the KIR-HLA interactions involve different amino acids for each of KIR2DL1 and 2/3, consistent with the fact that KIR2DL1 will not bind the natural ligand for KIR2DL2/3 and vice versa. Thus, any alleged teaching in Shin *et al.* that an mAb should have its epitope in the HLA-binding region in p58 KIR would if anything have directed a person of skill in the art away from the idea of an antibody that bound both KIR2DL1 and KIR2DL2/3 and was able to neutralize KIR-mediated inhibition of NK cell cytotoxicity.

Thus, the combined teachings of Shin *et al.* in view of Kim *et al.* do not render obvious claims 88, 90 and 91 because: 1) there is no motivation in either reference to seek antibodies that bind to both KIR2DL1 and KIR2DL2/3 and neutralize KIR-mediated inhibition of cytotoxicity; and 2) one of ordinary skill in the art, in view of the combined teachings of the references, would not have had a reasonable expectation of success in making antibodies that bound to both KIR2DL1 and

to KIR2DL2/3 and neutralized KIR-mediated inhibition of NK cell cytotoxicity. Accordingly, Applicants respectfully assert that the Shin *et al.* and Kim *et al.* references do not render obvious the claimed invention and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 88-91 are rejected under 35 U.S.C. § 103(a) as obvious over Shin *et al.* (1999) in view of Kim *et al.* (1997) and by admissions in the specification on page 25 at lines 15-28 and at the paragraph spanning pages 25-26, and further in view of Harlow and Lane (1988). The Office Action claims that Harlow and Lane teach that PBS or similar isotonic solutions are commonly used buffers for storing purified antibodies. Applicants respectfully assert that the claimed invention is not obvious over the cited references. As discussed above, the combination of Shin *et al.* and Kim *et al.* fail to raise a *prima facie* case of obviousness for the claimed invention. The teachings of Harlow and Lane (directed to formulation of antibodies in pharmaceutically acceptable carriers) fail to remedy the defects, noted above, in the combined teachings of Shin *et al.* and Kim *et al.* Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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